

[54] 1,2,3,4-TETRAHYDRO-CARBAZOLE
COMPOUNDS AND β -ADRENERGIC
COMPOSITIONS

[75] Inventors: Herbert Leinert, Heppenheim;
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Stach, Mannheim-Waldhof;
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[73] Assignee: Boehringer Mannheim G.m.b.H.,
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[22] Filed: Apr. 16, 1975

[21] Appl. No.: 568,743

[30] Foreign Application Priority Data

May 21, 1974 Germany..... 2424523

[52] U.S. Cl..... 424/274; 260/315

[51] Int. Cl.²..... A61K 31/40

[58] Field of Search..... 260/315; 424/274

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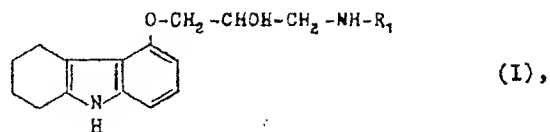
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Primary Examiner—Sherman D. Winters
Attorney, Agent, or Firm—Burgess, Dinklage &
Sprung

[57] ABSTRACT

New 1,2,3,4-tetra-hydrocarbazole derivatives of the
formula:



wherein R¹ is straight-chained or branched alkyl, and
the pharmacologically compatible salts thereof, are
markedly effective as inhibitors of adrogenic β -recep-
tors and thus useful for the treatment and prophylaxis
of cardiac and circulatory diseases.

13 Claims, No Drawings

United States Patent [19]

Zölss et al.

[11] Patent Number: 4,767,784

[45] Date of Patent: Aug. 30, 1988

[54] NOVEL CRYSTALLINE SALTS OF
ARYLOXY-PROPANOLAMINES, A
PROCESS FOR THEIR PREPARATION AND
THEIR USE

[76] Inventors: Gerhard Zölss, Ziegeleistrasse 72/2,
A-4020 Linz; Gerhard Pfarrhofer,
Schumpeterstrasse 15, A-4040 Linz,
both of Austria

[21] Appl. No.: 935,917

[22] Filed: Nov. 28, 1986

[30] Foreign Application Priority Data

Dec. 13, 1985 [DE] Fed. Rep. of Germany 3544172

[51] Int. Cl.⁴ A61K 31/17; C07C 127/19;
C07C 101/00

[52] U.S. Cl. 514/554; 260/501.11;
260/501.17; 260/501.18; 260/502 R; 514/555;
514/561; 514/563; 514/564; 514/576; 560/19;
560/29; 560/101; 562/471; 562/472; 562/480;
562/490; 562/493; 564/51; 564/52; 564/164;
564/165; 564/169; 564/336; 564/347; 558/303;
558/308

[58] Field of Search 564/51, 52, 164, 165,
564/169, 336, 347; 560/101, 19, 29; 260/501.17,
501.11, 501.18, 502; 562/472, 471, 480, 490,
493; 514/554, 555, 561, 563, 564, 576; 558/303,
308

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Chemical Abstracts; vol. 102 (1985) Nr. 72332g.

Primary Examiner—Glennon H. Hollrah

Assistant Examiner—Raymond Covington

[57]

ABSTRACT

The invention relates to novel crystalline salts of aryloxypropanolamines with diphenylacetic acid, a process for their preparation and the use of these salts for the preparation of chemically pure aryloxy-propanolamines or pharmaceutically acceptable salts thereof.

4 Claims, No Drawings

United States Patent [19]

Zöl et al.

[11] Patent Number: 4,849,530

[45] Date of Patent: Jul. 18, 1989

- [54] PROCESS FOR THE PREPARATION OF
CRYSTALLINE SALTS OR
ARYLOXY-PROPANOLAMINES
- [75] Inventors: Gerhard Zöl; Gerhard Pfarrhofer,
both of Linz, Austria
- [73] Assignee: Rorer Pharmaceutical Corporation,
Fort Washington, Pa.
- [21] Appl. No.: 203,390
- [22] Filed: Jun. 6, 1988

Related U.S. Application Data

- [62] Division of Ser. No. 935,917, Nov. 28, 1986, Pat. No.
4,767,784.

[30] Foreign Application Priority Data

- Dec. 13, 1985 [DE] Fed. Rep. of Germany 3544172
- [51] Int. Cl.⁴ C07C 127/19; C07C 101/00
- [52] U.S. Cl. 549/491; 558/303;
558/308; 560/19; 560/20; 560/101; 562/471;
562/472; 562/486; 562/490; 562/492; 562/491;
564/51; 564/52; 564/164; 564/165; 564/336;
564/347
- [58] Field of Search 564/51, 52, 164, 165,
564/169, 336, 347; 260/501.17, 501.11, 501.18,
502; 558/303, 308; 549/491; 560/19, 20, 101;
562/471, 472, 486, 490, 493

[56] References Cited

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- 3,501,769 3/1970 Crowther et al. 260/501.17
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1383899 2/1975 United Kingdom 564/51
1396322 6/1975 United Kingdom 564/51

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Med. Chem (19/2), vol. 15, 45-48.
Bartsch et al.; Arzneimittel-Forsch, 27(1) Nr. 5 (1977),
1022-1026 Chemical Abstracts; vol. 102 (1985), No.
72332 g.

Primary Examiner—Richard L. Raymond
Assistant Examiner—Raymond Covington

[57] ABSTRACT

The invention relates to novel crystalline salts of aryloxypropanolamines with diphenylacetic acid, a process for their preparation and the use of these salts for the preparation of chemically pure aryloxy-propanolamines or pharmaceutically acceptable salts thereof.

4 Claims, No Drawings

Mai et al.

[11] Patent Number: 4,990,668

[45] Date of Patent: Feb. 5, 1991

- [54] **OPTICALLY ACTIVE
ARYLOXYPROPANOLAMINES AND
ARYLETHANOLAMINES**
- [75] **Inventors:** Khuong H. X. Mai, Waukegan;
Ghanshyam Patil, Vernon Hills;
William L. Matier, Libertyville, all of
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- [73] **Assignee:** E. I. Du Pont de Nemours and
Company, Wilmington, Del.
- [21] **Appl. No.:** 804,407
- [22] **Filed:** Dec. 4, 1985
- [51] **Int. Cl.⁵** C07C 215/08; C07C 217/54
- [52] **U.S. Cl.** 564/349; 544/134;
544/169; 544/224; 544/312; 546/159; 548/135;
548/186; 548/247; 548/305; 548/444; 548/503;
548/509; 548/515; 549/23; 549/289; 549/304;
549/387; 549/466; 549/468; 549/487; 549/491;
558/401; 558/422; 560/29; 560/38; 560/42;
564/51; 564/79; 564/86; 564/165; 564/220;
564/363
- [58] **Field of Search** 544/134, 169, 224, 312;
546/158; 548/135, 186, 247, 305, 444, 503, 504,
515; 549/23, 289, 304, 387, 466, 468, 487, 491;
558/401, 422; 560/29, 35, 42; 564/51, 86, 165,
220, 79, 363, 349

[56] **References Cited**

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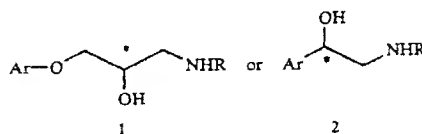
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Iriuchijima et al., "Agric. Biol. Chem.", vol. 46, No. 5, pp. 1153-1157 (1982).

Primary Examiner—Richard L. Raymond
Attorney, Agent, or Firm—Gildo E. Fato

[57] ABSTRACT

Described is a process for preparing a racemic or chiral aryloxypropanolamine (1) or arylethanolamine (2) of the formula



wherein Ar is aryl, substituted aryl, heteroaryl, or aralkyl and R is alkyl, substituted alkyl, aralkyl, or WB wherein W is a straight or branched chain alkylene of from 1 to about 6 carbon atoms and wherein B is $-\text{NR}_2\text{COR}_3$, $-\text{NR}_2\text{CONR}_3\text{R}_4$, $-\text{NR}_2\text{SO}_2\text{R}_3$, $-\text{NR}_2\text{SO}_2\text{NR}_3\text{R}_4$, or $-\text{NR}_2\text{COOR}_5$, where R_2 , R_3 , R_4 , and R_5 may be the same or different and may be hydrogen, alkyl, alkoxyalkyl, alkoxyaryl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, or aralkyl, except that R_3 and R_5 are not hydrogen when B is $-\text{NR}_2\text{SO}_2\text{R}_3$ or $-\text{NR}_2\text{COOR}_5$, or R_3 and R_4 may together with N form a 5- to 7-membered heterocyclic group.

The process can be used to prepare beta-blocking agents, useful in the treatment of cardiac conditions.

7 Claims, No Drawings

[54] PROCESS FOR THE PREPARATION OF OPTICALLY-ACTIVE CARBAZOLE DERIVATIVES, NEW R- AND S-CARBAZOLE DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THESE COMPOUNDS

[75] Inventor: Herbert Leinert, Heppenheim, Fed. Rep. of Germany

[73] Assignee: Boehringer Mannheim GmbH, Mannheim, Fed. Rep. of Germany

[21] Appl. No.: 631,641

[22] Filed: Jan. 28, 1991

Related U.S. Application Data

[62] Division of Ser. No. 299,750, Jan. 19, 1989, Pat. No. 4,985,454.

[30] Foreign Application Priority Data

May 26, 1983 [DE] Fed. Rep. of Germany 3319027

[51] Int. Cl.⁵ A61K.31/40; C07D 209/82; C07D 401/12; C07D 491/056

[52] U.S. Cl. 514/411; 514/302; 514/339; 514/913; 514/929; 546/115; 546/116; 546/272; 548/444

[58] Field of Search 548/444; 546/115, 116, 546/272; 514/302, 339, 411, 929, 913

[56] References Cited

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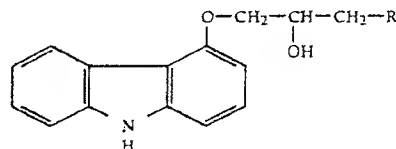
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Primary Examiner—Richard L. Raymond

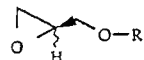
Assistant Examiner—P. O'Sullivan
Attorney, Agent, or Firm—Felfe & Lynch

[57] ABSTRACT

A process for the preparation of S- or R-carbazole derivatives of the general formula:



in which R is an unsubstituted or substituted amino radical and pharmacologically acceptable salts, by either reacting R-(−)-epichlorohydrin (for the S-carbazole derivative); or reacting an S-epoxide derivative of the general formula:



in which R₁ is the residue of a substituted sulphonic acid derivative (for the R-carbazole derivative); with 4-hydroxycarbazole and then with ammonia or a substituted amine of the general formula RH, and recovering the compound or converting it to a pharmacologically acceptable salt.

The new R-(+)- and S(−)-carbazole derivatives provided by the inventive process have unexpected beta blocking and vasodilatory properties and are useful in pharmaceutical compositions. R-(+)-carbazole derivatives are also useful for the treatment of glaucoma.

6 Claims, No Drawings



US006140352A

United States Patent [19]

[11] Patent Number: 6,140,352

Crowell et al.

[45] Date of Patent: *Oct. 31, 2000

- [54] CARBAZOLYL-SUBSTITUTED
ETHANOLAMINES AS SELECTIVE β_3
AGONISTS
- [75] Inventors: Thomas A. Crowell; Deborah A.
Evrard; Charles D. Jones; Brian S.
Muehl, all of Indianapolis; Christopher
J. Rito, Mooresville; Anthony J.
Shuker, Indianapolis, all of Ind.;
Andrew J. Thorpe, Ann Arbor, Mich.;
Kenneth J. Thrasher, Indianapolis,
Ind.
- [73] Assignee: Eli Lilly and Company, Indianapolis,
Ind.
- [*] Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

- [21] Appl. No.: 09/068,192
- [22] PCT Filed: Aug. 28, 1997
- [86] PCT No.: PCT/US97/15230
- § 371 Date: May 4, 1998
- § 102(e) Date: May 4, 1998
- [87] PCT Pub. No.: WO98/09625
- PCT Pub. Date: Mar. 12, 1998

Related U.S. Application Data

- [60] Provisional application No. 60/025,818, Sep. 5, 1996, and provisional application No. 60/029,228, Oct. 30, 1996.
- [51] Int. Cl.⁷ A61K 31/4439; C07D 401/12
- [52] U.S. Cl. 514/339; 514/323; 514/411;
514/374; 514/397; 514/381; 546/200; 546/276.7;
548/238; 548/252; 548/311.4; 548/444
- [58] Field of Search 546/276.7, 200;
548/444, 238, 252, 311.4; 514/323, 339,
411, 374, 397, 381

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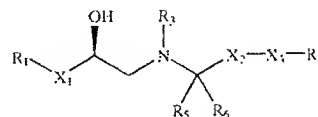
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(List continued on next page.)

Primary Examiner—Laura L. Stockton
Attorney, Agent, or Firm—Gilbert T. Voy

[57] ABSTRACT

Disclosed herein are selective beta 3 adrenergic agonists represented by the following structural formula:



The variables in the structural formula shown above are defined in the specification. Also disclosed are methods of using these compounds for agonizing the beta 3 adrenergic receptor in patients in need of such treatment, for example, patients in need of treatment for obesity or Type II diabetes.

41 Claims, No Drawings



US006939986B2

(12) **United States Patent**
Karpf et al.

(10) Patent No.: **US 6,939,986 B2**
(45) Date of Patent: **Sep. 6, 2005**

(54) **PROCESS FOR PREPARING 1,2-DIAMINO COMPOUNDS**

(75) Inventors: **Martin Karpf, Reinach (CH); René Trussardi, Birsfelden (CH)**

(73) Assignee: **Hoffmann-La Roche Inc., Nutley, NJ (US)**

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/081,345**

(22) Filed: **Feb. 22, 2002**

(65) **Prior Publication Data**

US 2002/0095040 A1 Jul. 18, 2002

Related U.S. Application Data

(62) Division of application No. 09/590,317, filed on Jun. 8, 2000.

(30) **Foreign Application Priority Data**

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Feb. 21, 2000 (EP) 00103588

(51) Int. Cl.⁷ **C07C 227/08; C07C 247/14; C07D 317/44**

(52) U.S. Cl. **560/29; 560/125; 560/128; 560/169; 546/146; 549/436; 549/546; 549/961; 514/237.5; 514/351; 514/454; 564/135; 548/477**

(58) Field of Search **560/125, 128, 560/169, 29; 549/436, 546, 961; 546/146; 514/237.5, 351, 454; 564/135; 548/477**

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Primary Examiner—James O. Wilson

Assistant Examiner—Devesh Khare

(74) *Attorney, Agent, or Firm*—George W. Johnston; Dennis P. Tramalon; Samuel H. Megerditchian

(57) **ABSTRACT**

The invention provides a multistep process for preparing 1,2-diamino compounds and pharmaceutically acceptable addition salts thereof from 1,2-epoxides.

2 Claims, No Drawings

Synthesis and Crystal Structure of Carvedilol

CHEN Wei-Min¹ ZENG Long-Mei² YU Kai-Bei³ XU Ji-Hong¹

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ABSTRACT The crystal structure of the title compound carvedilol, $C_{24}H_{25}N_2O_4$ ($M_r = 406.47$), has determined by single-crystal X-ray diffraction. The crystal is monoclinic with space group $P2_1/c$, $a=9.094(1)$, $b=12.754(1)$, $c=18.330(2)$ Å, $\beta=97.36(1)^\circ$, $V=2108.5(4)$ Å³, $Z=4$, $D_c=1.280$ g/cm³, $F(000)=864$, $\mu=0.088$ mm⁻¹ and final $R=0.0368$, $wR(F^2)=0.0787$ for reflections ($I>2\sigma(I)$). X-ray analysis reveals that the crystal is composed of a pair of enantiomer, and there are hydrogen bonds O(3)—H(30)—N(1) between the two enantiomers. There are two planes in the molecule.

Keywords: carvedilol, synthesis, crystal structure

1 INTRODUCTION

Carvedilol, 1-(4-carbazolyloxy)-3-[(2-methoxyphenoxy) ethylamino]-2-propanol, is a new β -blocking and vasodilating agent⁽¹⁾. It had synthesized by F. Wiedemann *et al*⁽²⁾. However the report about crystal structure of carvedilol has not been seen. In this paper, we discuss the crystal structure of the carvedilol synthesized⁽²⁾ by the reaction of 4-(2,3-epoxypropoxy)-carbazole and 2-(2-methoxyphenoxy) ethylamine. Since knowledge of the molecular and crystal structure of carvedilol was considered useful for understanding the mechanism of the action on the receptor, the X-ray crystallographic study was carried out.

2 EXPERIMENTAL

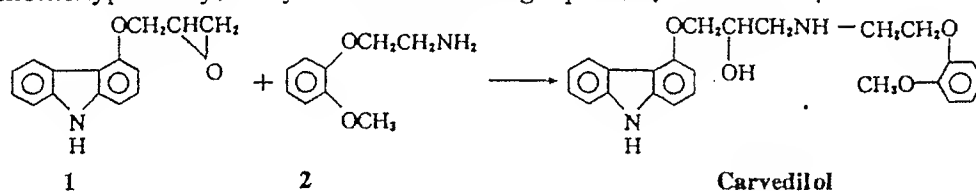
2.1 Synthesis⁽²⁾ 4-(2,3-Epoxypropoxy)-carbazole (10g, 42mmol) and 2-(2-methoxyphenoxy)-ethylamine (10g, 60 mmol) in 50 ml glycol dimethyl ether were stirred for 25 h at 50 °C. The reaction mixture was evaporated to dryness in a Rotavapor and the residue was stirred in 115ml toluol, 35 ml cyclohexane and 40 ml ethyl acetate, and recrystallized from ethyl acetate with the use of active charcoal. 10.4 g (61%) of the title compound were afforded. The single crystals suitable for X-ray analysis were obtained from the mixture solvent of toluol, cyclohexane and

ethyl acetate. mp: 114~115 °C; Calcd. for $C_{24}H_{26}N_2O_4$: C, 70.92; H, 6.45; N, 6.89. Found C, 70.75; H, 6.60; N, 6.72. IR(KBr): ν (N—H, O—H) 3346(s), (aryl-H) 3087(w), 1609(s), 1588(s), 1503(s), 1447(s) cm^{-1} . NMR: δ_H 1.8 (s, 2H, O—H, N₍₁₎—H), 3.1 (m, 4H, C₍₉₎H₂NC₍₁₀₎H₂), 3.8 (s, 3H, OCH₃), 4.2 (m, 5H, C₍₁₂₎H₂C₍₁₁₎H, C₍₈₎H₂), 6.7 (d, 1H, C₍₁₅₎H), 6.9 (s, 4H, C₍₃₋₆₎H₄), 7.1 (d, 1H, C₍₁₆₎H), 7.4~7.2 (m, 4H, C₍₂₂₋₂₄₎H₃), 8.20 (d, 1H, N₍₂₎H), 8.30 (d, 1H, C₍₁₄₎H). MS: m/z 406.2(M⁺, 17.7%).

2.2 Structure determination A single crystal with dimensions of 0.66mm × 0.52mm × 0.52mm was selected for X-ray diffraction analysis. All intensity data were collected on a Siemens P₄ diffractometer with graphite monochromated MoK α (λ = 0.71073 Å) radiation using ω scan mode. A total of 4081 reflections were collected in the range of $1.95 < \theta < 24.96^\circ$ at the temperature of 295 K, of which 2096 independent observed reflections with $I > 2\sigma(I)$ were used in the structure determination and refinement. The structure was solved by direct methods and succeeding difference Fourier synthesis. A full-matrix least-squares refinement gave final R = 0.0368 and wR = 0.0787 with $W = 1/[\sigma^2(F_o)^2 + (0.0501P)^2]$ and $P = [\max(F_o^2, O) + 2F_c^2]/3$, $(\Delta/\sigma)_{\max} = 0.004$, $S = 0.860$. The program for structure solution and refinement is SHELXTL 5.03.

3 RESULTS AND DISCUSSION

The title compound was prepared from 4-(2,3-epoxypropoxy)-carbazole and 2-(2-methoxyphenoxy) ethylamine as following equation:



The ORTEP plot of the carvedilol with the H atoms is shown in Fig. 1. The unit cell packing of the carvedilol is shown in Fig. 2. Atomic coordinates and thermal parameters are listed in Table 1. The selected bond lengths and angles are given in Table 2 and Table 3, respectively.

Fig. 2 shows that the crystal is composed of a pair of enantiomers, C(11) is a chiral carbon. The angle of O(3)—C(11)—C(10) is $110.5(2)^\circ$, that of C(12)—C(11)—C(10) is $110.4(2)^\circ$, which are larger than normal $109.5(2)^\circ$, the angle of O(3)—C(11)—C(12) is 107.13° , which is slightly less than normal 109.5° . The atoms C(1), O(1), C(2), C(3), C(4), C(5), C(6), C(7) are on one plane, plane equation: $-2.846X + 12.021Y - 1.391Z + 4.9410 = 0$. While the atoms C(13), C(14), C(15), C(16), C(17), C(18), N(2), C(19), C(20), C(21),

C(22), C(23), C(24) are on the another plane. plane equation $-2.470X + 11.564Y - 5.228Z + 2.1566 = 0$.

Table 1. Atomic Coordinates and Thermal Parameters (\AA^2)

Atom	x	y	z	Ueq	Atom	x	y	z	Ueq
O(1)	0.6502(1)	-0.2750(1)	-0.1120(1)	0.069	C(10)	0.5423(2)	-0.0937(2)	0.1254(1)	0.061
O(2)	0.8405(1)	-0.2127(1)	-0.0057(1)	0.067	C(11)	0.4035(2)	-0.0314(2)	0.0987(1)	0.056
O(3)	0.3346(2)	-0.0714(1)	0.0299(1)	0.075	C(12)	0.2915(2)	-0.0409(2)	0.1528(1)	0.050
O(4)	0.3617(1)	-0.0015(1)	0.2218(1)	0.061	C(13)	0.2817(2)	0.0031(1)	0.2803(1)	0.055
N(1)	0.6482(2)	-0.0943(1)	0.0719(1)	0.058	C(14)	0.1396(2)	-0.0352(2)	0.2810(1)	0.070
N(2)	0.3756(2)	0.1060(1)	0.4609(1)	0.068	C(15)	0.0697(2)	-0.0232(2)	0.3439(1)	0.080
C(1)	0.5335(3)	-0.2973(3)	-0.1699(2)	0.096	C(16)	0.1358(2)	0.0251(2)	0.4059(1)	0.078
C(2)	0.7837(2)	-0.2442(1)	-0.1312(1)	0.054	C(17)	0.2802(2)	0.0608(1)	0.4056(1)	0.058
C(3)	0.8180(3)	-0.2439(2)	-0.2018(1)	0.073	C(18)	0.3543(2)	0.0498(1)	0.3436(1)	0.049
C(4)	0.9535(3)	-0.2108(2)	-0.2156(1)	0.088	C(19)	0.5017(2)	0.0899(1)	0.3632(1)	0.049
C(5)	1.0573(3)	-0.1773(2)	-0.1605(2)	0.084	C(20)	0.5114(2)	0.1234(1)	0.4368(1)	0.056
C(6)	1.0243(2)	-0.1758(2)	-0.0875(1)	0.070	C(21)	0.6419(3)	0.1617(2)	0.4745(1)	0.072
C(7)	0.8873(2)	-0.2091(1)	-0.0737(1)	0.052	C(22)	0.7628(3)	0.1668(2)	0.4378(1)	0.079
C(8)	0.8994(2)	-0.1381(2)	0.0482(1)	0.065	C(23)	0.7563(2)	0.1371(2)	0.3648(1)	0.072
C(9)	0.7931(2)	-0.1338(2)	0.1041(1)	0.064	C(24)	0.6274(2)	0.0986(2)	0.3270(1)	0.059

U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor

Table 2. Selected Bond Lengths (\AA)

Bond	Dist.	Bond	Dist.	Bond	Dist.	Bond	Dist.
O(1)—C(1)	1.429(3)	N(2)—C(17)	1.374(2)	C(8)—C(9)	1.497(3)	C(17)—C(18)	1.400(2)
O(1)—C(2)	1.365(2)	N(2)—C(20)	1.382(2)	C(10)—C(11)	1.518(2)	C(18)—C(19)	1.437(2)
O(2)—C(7)	1.368(2)	C(2)—C(3)	1.370(2)	C(11)—C(12)	1.514(2)	C(19)—C(20)	1.407(2)
O(2)—C(8)	1.424(2)	C(2)—C(7)	1.394(2)	C(13)—C(14)	1.383(2)	C(19)—C(24)	1.398(2)
O(3)—C(11)	1.430(2)	C(3)—C(4)	1.357(3)	C(13)—C(18)	1.394(2)	C(20)—C(21)	1.384(2)
O(4)—C(12)	1.431(2)	C(4)—C(5)	1.360(3)	C(14)—C(15)	1.395(3)	C(21)—C(22)	1.362(3)
O(4)—C(13)	1.372(2)	C(5)—C(6)	1.408(3)	C(15)—C(16)	1.363(3)	C(22)—C(23)	1.385(3)
N(1)—C(9)	1.462(2)	C(6)—C(7)	1.371(2)	C(16)—C(17)	1.391(3)	C(23)—C(24)	1.374(2)
N(1)—C(10)	1.459(2)						

Table 3. Selected Bond Angles ($^\circ$)

Angle	($^\circ$)	Angle	($^\circ$)	Angle	($^\circ$)
C(1)—O(1)—C(2)	117.9(2)	O(2)—C(8)—C(9)	106.3(2)	C(16)—C(17)—C(18)	121.6(2)
C(7)—O(2)—C(8)	118.40(14)	N(1)—C(9)—C(8)	111.4(2)	C(13)—C(18)—C(17)	119.5(2)
C(12)—O(4)—C(13)	118.95(14)	N(1)—C(10)—C(11)	112.4(2)	C(13)—C(18)—C(19)	133.4(2)
C(9)—N(1)—C(10)	111.74(14)	O(3)—C(11)—C(10)	110.5(2)	C(17)—C(18)—C(19)	107.0(2)
C(17)—N(2)—C(20)	109.7(2)	O(3)—C(11)—C(12)	107.13(14)	C(18)—C(19)—C(20)	106.83(14)
O(1)—C(2)—C(3)	124.1(2)	C(10)—C(11)—C(12)	110.4(2)	C(18)—C(19)—C(24)	134.7(2)
O(1)—C(2)—C(7)	115.83(14)	O(4)—C(12)—C(11)	106.8(2)	C(20)—C(19)—C(24)	118.5(2)
C(3)—C(2)—C(7)	120.0(2)	O(4)—C(13)—C(14)	125.6(2)	N(2)—C(20)—C(19)	108.0(2)
C(2)—C(3)—C(4)	119.9(2)	O(4)—C(13)—C(18)	115.32(14)	N(2)—C(20)—C(21)	129.9(2)
C(3)—C(4)—C(5)	121.3(2)	C(14)—C(13)—C(18)	119.1(2)	C(19)—C(20)—C(21)	122.1(2)
C(4)—C(5)—C(6)	119.9(2)	C(13)—C(14)—C(15)	119.6(2)	C(20)—C(21)—C(22)	117.7(2)
C(5)—C(6)—C(7)	118.7(2)	C(14)—C(15)—C(16)	122.7(2)	C(21)—C(22)—C(23)	121.8(2)
O(2)—C(7)—C(2)	114.8(1)	C(15)—C(16)—C(17)	117.4(2)	C(22)—C(23)—C(24)	120.9(2)
O(2)—C(7)—C(6)	125.1(2)	N(2)—C(17)—C(16)	129.9(2)	C(19)—C(24)—C(23)	119.0(2)
C(2)—C(7)—C(6)	120.1(2)	N(2)—C(17)—C(18)	108.5(2)		

The X-ray crystallographic analysis shows that there is a hydrogen bond O(3)—H(30)—N(1) between the two enantiomers, the distance of O(3)—N(1) is 2.837

Å, and the bond length O(3)—H(3) is 1.139 Å, hydrogen bond length of H(30)—N(1) is 1.730 Å. The angle of O(3)—H(30)—N(1) is 173.1°.

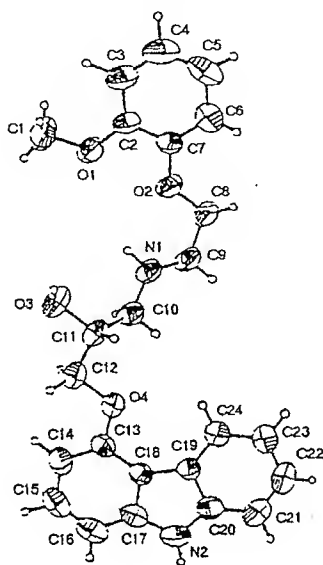


Fig. 1 Structure of carvedilol

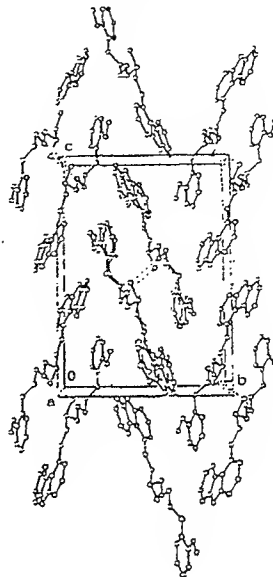


Fig. 2 Packing of the molecules in a unit cell

In vitro investigations with the purified stereoisomers of carvedilol show that β_1 -adrenoceptor blockade can be attributed primarily to the S(—)-enantiomer. In contrast, both enantiomers exhibit similar α_1 -adrenergic blocking activity^[3]. Thus, the configuration of chiral carbon C(11) is related to the structure of β_1 -adrenoceptor, and not related to the structure of α_1 -adrenoceptor. The following illustration was thought^[4] as structure-activity relationship of carvedilol. The data of this paper will be useful for understanding the activity center of α_1 -adrenoceptor and β_1 -adrenoceptor.

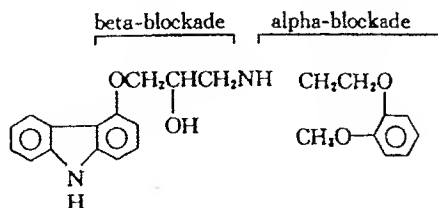


Fig. 3 Structure-activity relationship of carvedilol

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